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(54) Title: METHODS FOR TREATING VISUAL DISORDERS

(57) Abstract: The present invention provides methods for treating visual disorders. Exemplary visual disorders include macular degeneration, retinitis pigmentosa, glaucoma, and/or retinal degeneration.

METHODS FOR TREATING VISUAL DISORDERS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 60/651,729, filed February 10, 2005, which is incorporated herein by reference in its entirety.

SUMMARY

The present invention provides methods for treating visual disorders. Exemplary visual disorders include macular degeneration, retinitis pigmentosa, glaucoma, and/or retinal degeneration.

In one embodiment, a method includes administering to a subject a compound selected from the group of a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof. In one embodiments, the hydrophilic bile acid is ursodeoxycholic acid. In one embodiment, the compound administered is glycol- or tauro- ursodeoxycholic acid. In one embodiment, the compound is administered in combination with a pharmaceutically acceptable carrier.

In one embodiment, the method includes contacting an eye of a subject a compound selected from the group of a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof, wherein the visual disorder is macular degeneration, retinitis pigmentosa, glaucoma, and/or retinal degeneration

In one embodiment, administering to a subject includes contacting the eye of the subject with a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof.

In one embodiment, administering involves administering parenterally. In one embodiment, administering involves administering the compound in eye drops.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The words "preferred" and "preferably" refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the invention.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

BRIEF DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Fig. 1. Study design.

Fig. 2. A representative image of the retinal degeneration shown in sequential histophathologic images representative of the time point based on days from birth, and the influence of TUDCA.

Fig. 3. Data showing animals treated the TUDCA as compared to vehicle controls (see week 7, 10, and 12).

Fig. 4. Data showing a trend toward a protective effect of TUDCA on the rate of retinal degeneration.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides methods that involve the treatment of visual disorders, including macular degeneration, retinitis pigmentosa, glaucoma, retinal degeneration (e.g., rod photoreceptor degeneration).

The methods of the present invention involve administering to a subject (particularly, contacting the eye of a subject) with a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof. As used herein, hydrophilic bile acids are those more hydrophilic than deoxycholic acid (DCA). This can be determined by evaluating the partition coefficient between water and octanol, with the more hydrophilic bile acids being more favorable toward water. Alternatively, the more hydrophilic bile acids have earlier retention times on a reverse-phase column using high performance liquid chromatography. A particularly preferred hydrophilic bile acid includes ursodeoxycholic acid. Examples of analogs of hydrophilic bile acids include conjugated derivatives of bile acids. Two particularly preferred conjugated derivatives include glyco- and tauro-ursodeoxycholic acid.

Although all hydrophilic bile acids may not be useful in all methods of the present invention, they can be evaluated readily by a method similar to that mentioned above. Such compounds are used in amounts effective to treat (including prevent) a visual disorder, whether it be prophylactically or therapeutically. They can be used in the methods of the present invention in the form of a composition that also includes a pharmaceutically acceptable carrier, if so desired. Typically, for preferred embodiments, the compounds described herein are formulated in pharmaceutical compositions, and then, in accordance with methods of the invention, administered to a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration. The formulations include those particularly suitable for ophthalmic administration (e.g., eye drops) or other local methods, although other modes of administration such as oral or parenteral (including subcutaneous, intramuscular, intraperitoneal and intravenous) administration may be possible. Local drug delivery methods include subtenon's, subconjunctival, intravitreal, topical, suprachoroidal, peribulbar, or from a local delivery device that utilizes the transscleral route. Treatment can be prophylactic, or alternatively, can be initiated after diagnosis of the visual disorder. That is, compounds of the present invention can be used to prevent the onset and/or progression of a visual disorder.

The formulations may be conveniently presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All

methods include the step of bringing the active compound into association with a carrier that constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into a desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as tablets, troches, capsules, lozenges, wafers, implants, or cachets, each containing a predetermined amount of the compound as a powder, in granular form, incorporated within liposomes, or as a solution or suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion, or a draught. Such compositions and preparation should contain at least about 500 mg/day to about 1000 mg/day, or alternatively stated, about 10 mg/kg body weight to about 15 mg/kg body weight.

The tablets, troches, pills, capsules, and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, fructose, lactose or aspartame; and a natural or artificial flavoring agent. When the unit dosage form is a capsule, it may further contain a liquid carrier, such as a vegetable oil, a polyethylene glycol, in poly(ortho esters), or poly(lactic-co–glycolic) acid microspheres. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, or sugar, and the like. A syrup or elixir may contain one or more of a sweetening agent, a preservative such as methyl- or propylparaben, an agent to retard crystallization of the sugar, an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol, for example glycerol or sorbitol, a dye, and flavoring agent. The material used in preparing any unit dosage form is substantially nontoxic in the amounts employed. The compound may be incorporated into sustained-release preparations and devices.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the compound, or dispersions of sterile

powders comprising the compound, which are preferably isotonic with the blood of the recipient. Isotonic agents that can be included in the liquid preparation include sugars, buffers, and salts such as sodium chloride. Solutions of the compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions of the compound can be prepared in water, ethanol, a polyol (such as glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, glycerol esters, and mixtures thereof. The ultimate dosage form is sterile, fluid, and stable under the conditions of manufacture and storage. The necessary fluidity can be achieved, for example, by using liposomes, by employing the appropriate particle size in the case of dispersions, or by using surfactants. Sterilization of a liquid preparation can be achieved by any convenient method that preserves the bioactivity of the compound, preferably by filter sterilization. Preferred methods for preparing powders include vacuum drying and freeze drying of the sterile injectible solutions. Subsequent microbial contamination can be prevented using various antimicrobial agents, for example, antibacterial, antiviral and antifungal agents including parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. Absorption of the compounds over a prolonged period can be achieved by including agents for delaying, for example, aluminum monostearate and gelatin.

Eye drop formulations are preferred and comprise purified aqueous solutions of the compound with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the eye.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredients including diluents, buffers, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

Useful dosages of the compounds described herein can be determined by comparing their in vitro activity and the in vivo activity in animal models. Methods for extrapolation of effective dosages in mice, and other animals, to humans are known in the art.

Generally, for adult humans, single dosages for injection, infusion, or ingestion will generally vary from about 500 mg to about 1000 mg (i.e., a dosage

of about 10 mg to about 15 mg per kg of body weight per day). It may be administered, for example, about 1 to about 3 times per day, to yield levels of about 10 to about 15 micromoles per liter of serum.

Advantages of the invention are illustrated by the following examples. However, the particular materials and amounts thereof recited in these examples, as well as other conditions and details, are to be interpreted to apply broadly in the art and should not be construed to unduly limit the invention.

EXAMPLES

Treatment of Neurosensory Retinal Degenerations with Bile Acid

We have studied the use of bile acids (tauroursodeoxycholic acid, TUDCA) for inhibition of neurosensory retinal degeneration in an animal model of retinal degeneration (P23H rat).

Retinal Degenerations: Age-Related Macular Degeneration (AMD) is the leading cause of blindness in the United States and Western World in individuals over age 50. Early changes of AMD are common. In fact, by age 65, nearly 25% of individuals will demonstrate signs of early AMD, while 1-2% will have late AMD or severe vision loss (Beaver Dam Eye Study, Beaver Dam Wisconsin, R. Klein *et al*). Inherited retinal degeneration (such as retinitis pigmentosa) is the leading cause of inherited blindness (estimated prevalence 1:3000). Despite an intense effort to develop new treatments, our existing therapies to treat these retinal degenerations are extremely limited. The exact mechanism involved in the loss of the neurosensory retina is unknown, but there is increasing evidence that apoptosis of the photoreceptors and the retinal pigment epithelium (RPE) is a primary mechanism. The P23H rat model represents a common protein conformational disease found in humans. Age-related macular degeneration is likely to also represent a 'multigenic' protein conformational disease. The mechanism of cellular injury in both conditions is likely mediated through apoptosis. Epidemiologic prevalence data in the population of Wisconsin (quite similar to Minnesota) is well characterized for AMD (Beaver Dam Wisconsin) and could be readily compared based on a standardized grading system.

Bile Acids: Bile acids are essential for emulsifying lipids in the intestinal lumen, and their synthesis and transport drive bile formation and provide a degradation pathway for cholesterol. More recently, Steer et al. have demonstrated that UDCA (ursodeoxycholic acid) and TUDCA will interrupt apoptosis by blocking classic pathways, and induction of survival pathways, demonstrated both *in vitro* and *in vivo*. Specifically, TUDCA has been demonstrated to be neuroprotective in animal models of Huntington's disease, improved graft survival in Parkinsonian rats, and protect against neurologic injury after acute ischemic or hemorrhagic stroke (Low & Steer et al.). Preliminary work done with the rds mouse model of inherited retinal degeneration, demonstrated a dramatic protection of the inner nuclear layer of the retina in this inherited form of neurosensory retinal degeneration. Functional preservation of the electroretinographic response (functional test of vision) also demonstrated preservation of visual function in the mouse model.

Animal Studies: The P23H rat model of inherited retinal degeneration is an animal model of a common mutation found in >10% of autosomal dominantly inherited retinitis pigmentosa in humans. This animal model has been studied in the laboratory of Dr. Olsen at the University of Minnesota. The mechanism of retinal degeneration is mediated by apoptosis, but may follow a separate pathway than that of the rds mouse. The P23H rat model represents a protein conformational disorder that leads to retinal degeneration. Other examples of protein conformation disorders include Huntington's and Parkinson's disease. The rds mouse degeneration is mediated largely through a mutation in the β-subunit of rod cGMP phoshodiesterease, leading to increased cGMP that is toxic to photoreceptors.

Preliminary Study: Homozygous line 1 and line 3 P23H rats (very strong model of rapid retinal degeneration, especially in the homozygous state), were given 100-200 mg/kg/d of TUDCA via subcutaneous injections while control animals will be given placebo vehicle only. Animals were sacrificed at intervals that correspond to the known retinal degenerations. Eyes were enucleated and the neurosensory retina was examined for signs of neuroprotection by counting the cell nuclei in the various retinal layers (Figure 1; study design). For each animal studied, 14 sections were taken for each eye with 30-50 separate

measurements performed and averaged for each section. Counting the average number of outer nuclear layer (ONL) cells was used to determine the level of retinal injury or loss.

A representative image of the retinal degeneration is shown in sequential histophathologic images representative of the time point based on days from birth, and the influence of TUDCA (Figure 2). Note that by week 12 in the TUDCA treated line 1 animals, that there is a visible difference in the thickness of the drug treated ONL as compared to the vehicle. In the line 3 animal study, there is less noticeable difference between the drug treated and the control. (A Sprague Dawley animal with no retinal degeneration is used as the control slide for comparison to a normal healthy animal.)

Using line 1 animals (Figure 3) there is no statistically significant differences at any time point after birth in animals treated the TUDCA as compared to vehicle controls (see week 7, 10, and 12). Additionally, animal weight recordings indicated a significant weight loss in treated animals as compared to controls by day 37 and beyond ($p<0.05$), suggesting systemic toxicity at these dosages.

Using line 3 animals (Figure 4), we were able to demonstrate and trend toward a protective effect of TUDCA on the rate of retinal degeneration by counting the ONL layer thickness at the 9 week post-natal time point ($p=0.16$). However, this did not reach statistical significance. In the line 1 animals, there was no statistically significant protective effect (Figure 4). Once again, animal weight recordings indicated a significant weight loss in treated animals as compared to controls by day 37 and beyond ($p<0.05$), suggesting systemic toxicity at these dosages.

Conclusions: This study indicates a trend toward protection in retinal degenerations in the P23H homozygous model. Using the P23H rat in a homozygous genetic state does not purely represent the human condition that is heterozygous. The less aggressive heterozygous model perhaps would perhaps be a better model to determine the effect of TUDCA on the degeneration of the P23H rat.

The complete disclosure of all patents, patent documents, and publications cited herein are incorporated by reference. The foregoing detailed description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention defined by the claims.

What is claimed is:

1. A method for treating a visual disorder, the method comprising administering to a subject a compound selected from the group of a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof.

2. The method of claim 1 wherein the hydrophilic bile acid is ursodeoxycholic acid.

3. The method of claim 1 wherein the compound administered is glycol- or tauro- ursodeoxycholic acid.

4. The method of claim 1 wherein the visual disorder is macular degeneration, retinitis pigmentosa, glaucoma, and/or retinal degeneration.

5. The method of claim 1 wherein administering to a subject comprises contacting the eye of the subject with a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof.

6. The method of claim 1 wherein the compound is administered in combination with a pharmaceutically acceptable carrier.

7. The method of claim 1 wherein administering comprises administering parenterally.

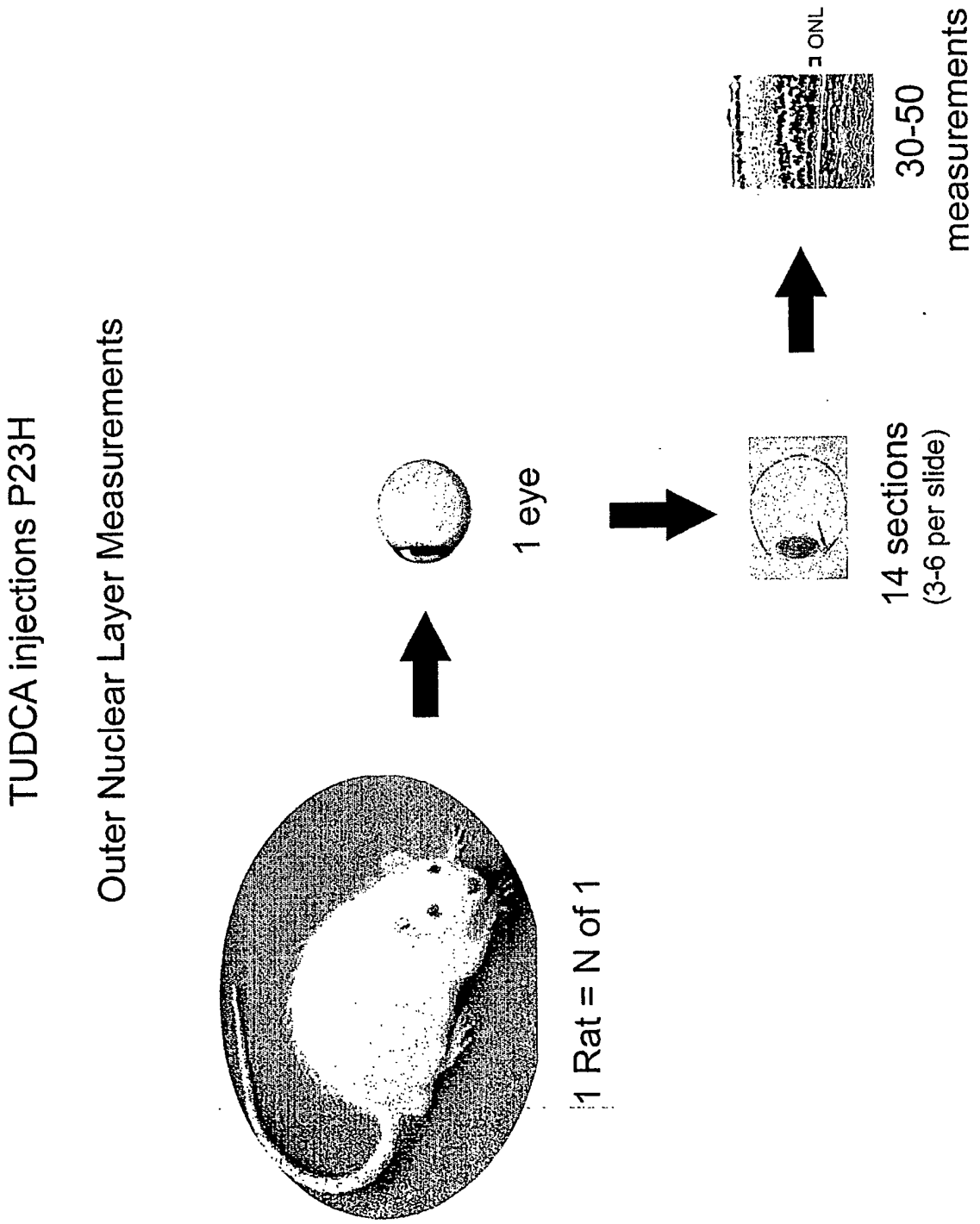
8. The method of claim 1 wherein administering comprises administering the compound in eye drops.

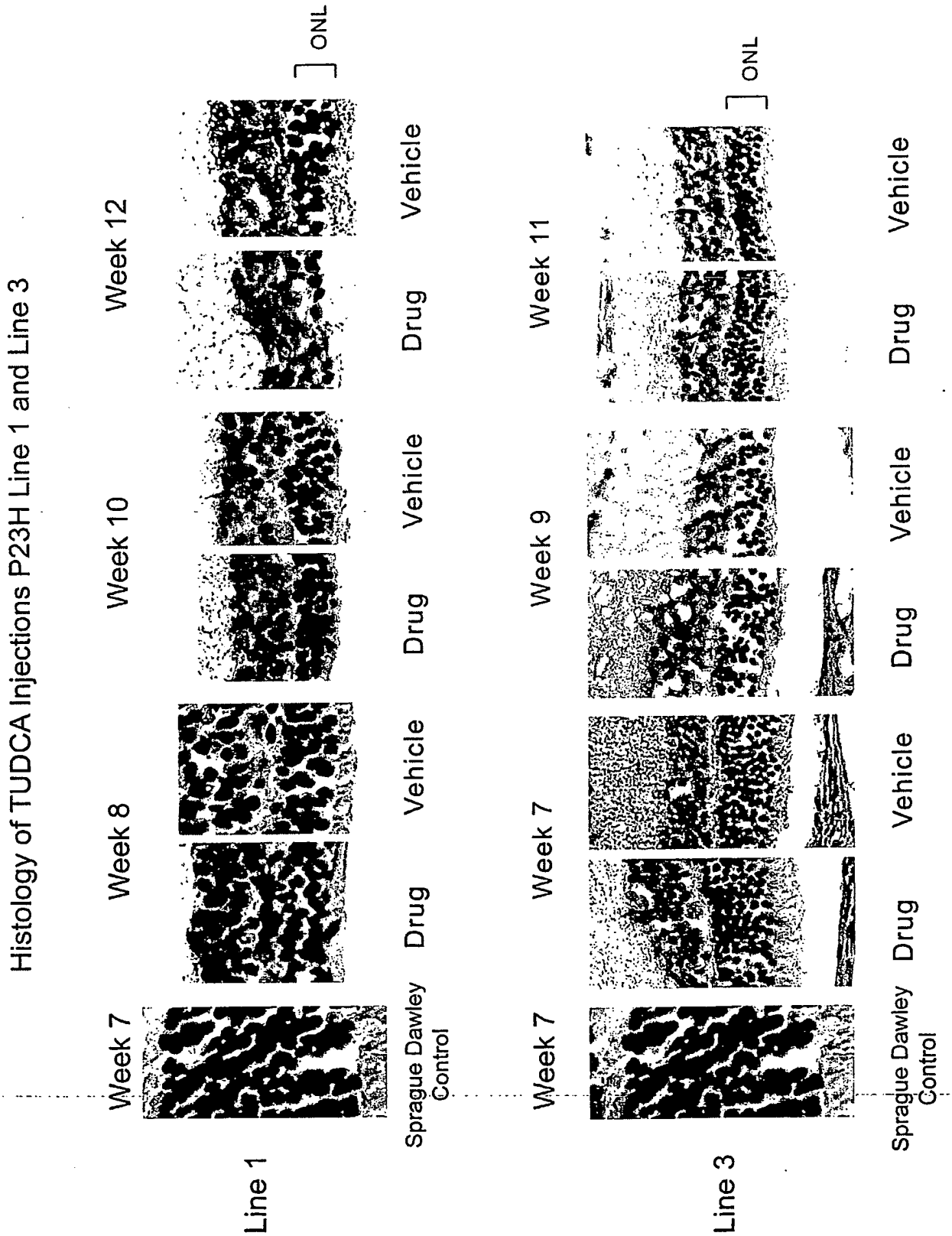
9. A method for treating a visual disorder, the method comprising contacting the eye of a subject a compound selected from the group of a hydrophilic bile acid, salts thereof, analogs thereof, or combinations thereof, wherein the visual disorder is macular degeneration, retinitis pigmentosa, glaucoma, and/or retinal degeneration.

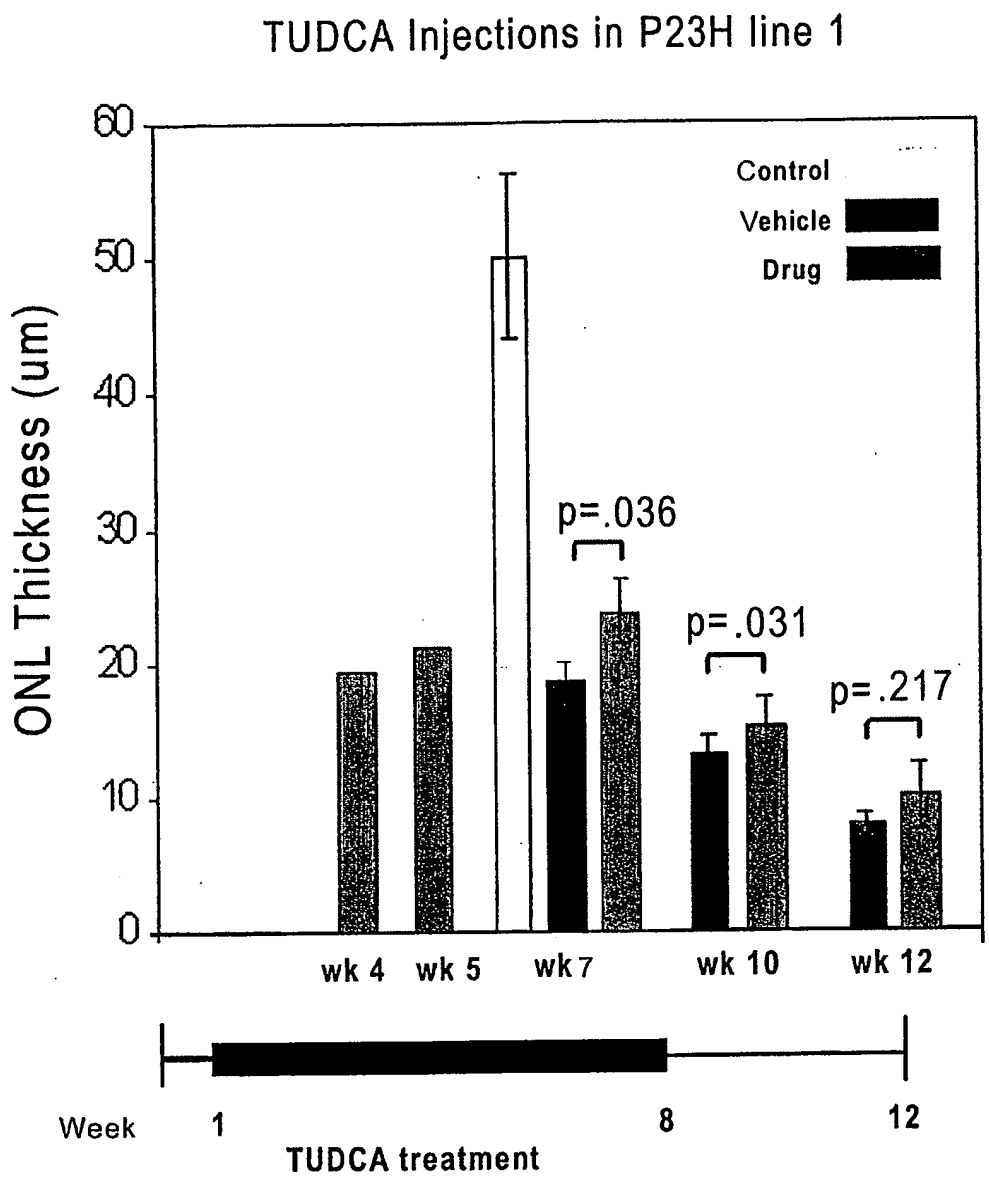
10. The method of claim 9 wherein the hydrophilic bile acid is ursodeoxycholic acid.

11. The method of claim 9 wherein the compound administered is glycol- or tauro- ursodeoxycholic acid.

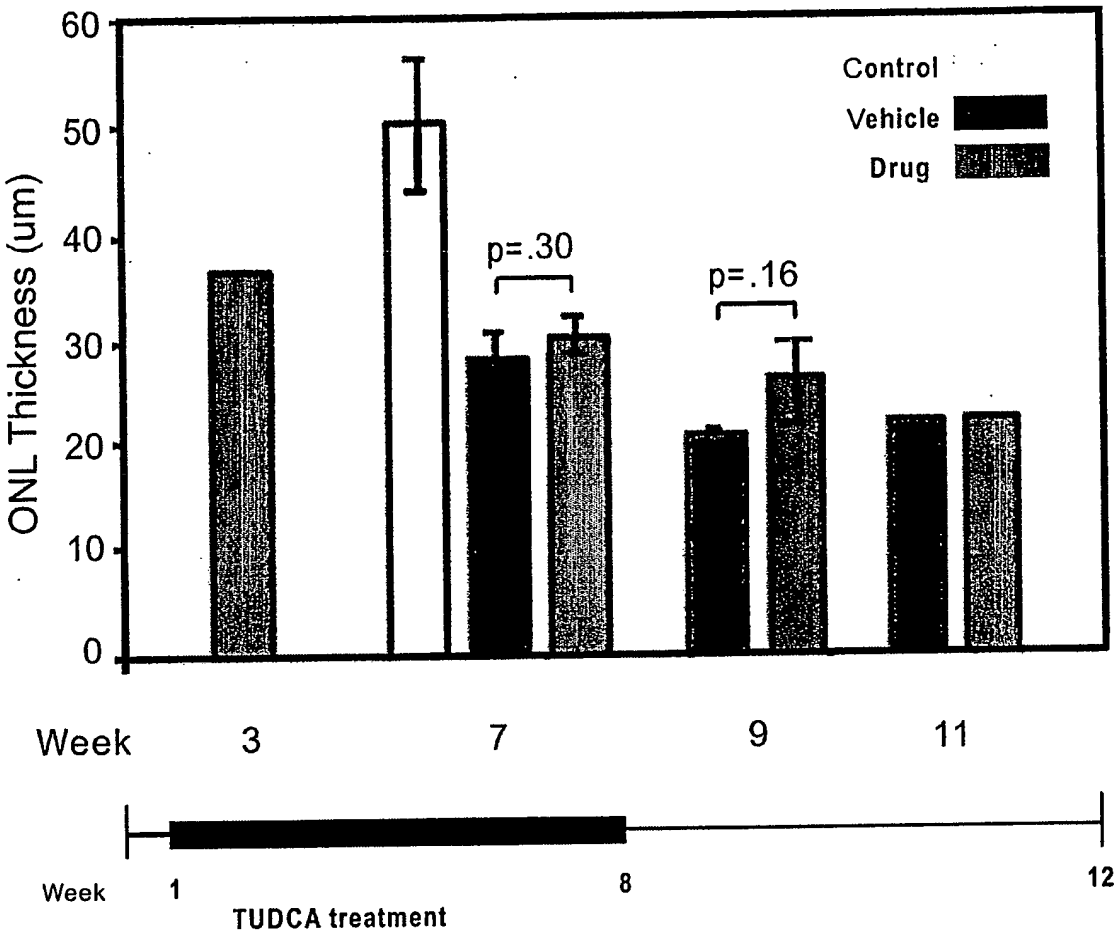
12. The method of claim 9 wherein administering comprises administering the compound in eye drops.


TUDCA injections P23H
Outer Nuclear Layer Measurements
1 Rat = N of 1
1 eye
14 sections
(3-6 per slide)
ONL
30-50
measurements


Histology of TUDCA Injections P23H Line 1 and Line 3
Line 1
Week 7
Week 8
Week 10
Week 12
Sprague Dawley Control
Drug
Vehicle
Drug
Vehicle
ONL
Line 3
Week 7
Week 9
Week 11
Sprague Dawley Control
Drug
Vehicle
Drug
Vehicle
ONL


TUDCA Injections in P23H line 1
ONL Thickness (um)
60
50
40
30
20
10
0
Control
Vehicle
Drug
p=.036
p=.031
p=.217
wk 4
wk 5
wk 7
wk 10
wk 12
Week
1
8
12
TUDCA treatment

TUDCA Injections in P23H Line 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/004394

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/575 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GERMAN MORING A J ET AL: "PROTECTIVE EFFECTS OF TAUROURSODEOXYCHOLIC ACID AGAINST OXIDATIVE DAMAGE IN HUMAN RETINOBLASTOMA CELLS." ARVO ANNUAL MEETING ABSTRACT SEARCH AND PROGRAM PLANNER, vol. 2003, 2003, page Abstract No. 4551, XP009068830 & ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY; FORT LAUDERDALE, FL, USA; MAY 04-08, 2003 abstract	1-12
X	WO 02/47694 A (FEHER, JANOS) 20 June 2002 (2002-06-20) page 17 - page 18; example 10	1-3,5-8

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 July 2006	28/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Loher, F

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	PHILLIPS J ET AL: "Tauroursodeoxycholic acid (TUDCA) preserves photoreceptor function and morphology in rd10 mice at post-natal day 30" IOVS, vol. 46, no. Suppl. S, 2005, page 5237, XP009068828 & ANNUAL MEETING OF THE ASSOCIATION-FOR-RESEARCH-IN-VISION-AND-OPHTHALM OLOGY; FT LAUDERDALE, FL, USA; MAY 01 -05, 2005 ISSN: 0146-0404 abstract	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/004394

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/004394

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0247694 A	20-06-2002	AU 1630102 A	24-06-2002
		CA 2445091 A1	20-06-2002
		EP 1408982 A1	21-04-2004
		JP 2004515532 T	27-05-2004
		US 2004038952 A1	26-02-2004